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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,300	02/24/2004	Roy A. Black	016761-0171	5048

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,300	BLACK ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-22 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-22 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-9, 11-22, and 28-31 are pending in the application.

[2] Applicant's amendment to the claims, filed on 12/22/06, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 12/22/06, is acknowledged.

[4] Receipt of an information disclosure statement, filed on 12/22/06, is acknowledged.

[5] Receipt of a sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, and an amendment directing the sequence listing into the specification, all filed on 12/22/06, is acknowledged.

Information Disclosure Statement

[6] All references cited in the information disclosure statement filed on 12/22/06 have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Sequence Compliance

[7] In order to perfect sequence compliance of the sequence listing filed on 12/22/06, applicant is required to submit a statement that the content of the paper and CRF copies of the sequence listing filed on 12/22/06 does not introduce new matter into the specification.

[8] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly the disclosed Table 1 at pp. 37-74 of the specification containing a list of atomic coordinates representing the disclosure of an amino acid sequence. Applicant should identify this sequence by a proper sequence identifier.

Claim Objections

[9] Claim 9 is objected to in the recitation of "diffracts to 2.0 Å." In order to improve form of the claim, it is suggested that applicant identify in the claim what is diffracted, which, according to the specification is clearly x-rays (specification at p. 35, lines 18-20).

[10] Claim 14 is objected to as being grammatically incorrect in the recitation of "the the crystal" and it is suggested that the noted phrase be replaced with "the crystal."

[11] Claims 18 and 31 are objected to in the recitation of "hydroxyamino carbonyl," which appears to be a misspelling of "hydroxyaminocarbonyl". It is suggested that applicant replace "hydroxyamino carbonyl" with "hydroxyaminocarbonyl".

Claim Rejections - 35 USC § 112, Second Paragraph

[12] The rejection of claim(s) 11-12 under 35 U.S.C. 112, second paragraph, as lacking antecedent basis in the recitation of "TACE catalytic domain (TCD) molecules" is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues TCD is described in the specification, is well-known in the art, and a crystal having four independent TCD molecules in the unit cell is disclosed in the specification.

Applicant's argument is not found persuasive. As noted in the prior Office action, the TCD molecules of claim 11 lack antecedent basis as the crystal of claim 1 is not required to have TCD molecules – instead, the claim 1 crystal is of a TACE polypeptide. Because the term lacks antecedent basis, its meaning is unclear. For example, is the term "TCD molecule" intended as being of the same scope as "TACE polypeptide" or is the term meant to limit the TACE polypeptide of the crystal of claim 1 to being only the catalytic domain of a TACE polypeptide? And, for example, if the latter interpretation,

what amino acids of a TACE polypeptide are considered to be a catalytic domain? It is suggested that applicant clarify the meaning of the claims.

[13] Claim(s) 5, 14, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 5 is confusing in that it is unclear as to how the polynucleotide as recited in the claim, which appears to encode a variant of SEQ ID NO:8, simultaneously encodes amino acids 1-477 of SEQ ID NO:8. It is suggested that applicant clarify the meaning of the claim.

[b] Claims 14 and 30 are confusing in the recitation of "crystal has the structure coordinates according to Table 1" as it would appear that the TACE polypeptide of the crystal and not the crystal itself has the structural coordinates of Table 1, particularly as the structural coordinates provide the Cartesian coordinates for atoms of the amino acids of a TACE polypeptide. It is suggested that applicant clarify the meaning of the claims.

[c] Claim 5 is confusing in the recitation of "Asn542 as set forth in SEQ ID NO:8" as there does not appear to be a position 542 of SEQ ID NO:8 in the sequence listing filed on 12/22/06. It is suggested that applicant clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

[14] Claim(s) 15-16 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

Claim 15 has been amended to recite the limitation "wherein the crystallization buffer comprises sodium citrate." According to applicant, support for claim 15 can be found at p. 33, line 21 to p. 34, line 9 (see instant response at p. 16, top). However, it is noted that the cited support fails to provide support for a generic crystallization buffer comprising sodium citrate. Instead, the cited support provides specific formulations and concentrations of components of specific crystallization buffers, which fail to provide support for the broader limitation as noted above. See MPEP 2163.05.I. Applicant is invited to show support in the specification, claims, and/or drawings for the limitation at issue.

[15] The written description rejection of claim(s) 1-9 and 11-22 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. Newly added claims 28-31 are included in the instant rejection. Thus, claims 1-9, 11-22, and 28-31 are rejected herein.

RESPONSE TO ARGUMENT: Applicant argues the rejection is obviated by amendment to claims 1 and 22 to recite the space group of the claimed crystal. According to applicant, since the polypeptide is disclosed, the recited characteristics are sufficient to describe the genus of claimed crystals in view of Case 4 of the Trilateral Report.

Applicant's argument is not found persuasive. The examiner acknowledges applicant's amendment to recite the space group of the crystal in claims 1 and 22. It is noted that the claim of Case 4 of the Trilateral Report recites unit cell dimensions, which is not present in the instant claims 1 and 22. Even in view of the amendment, the recited characteristics fail to provide sufficient distinguishing characteristics of the genus of claimed crystals such that a skilled artisan would recognize that applicant was in possession of the claimed invention. As noted in the prior Office action and undisputed by applicant, the specification discloses only a single representative species of the genus of recited or claimed TACE polypeptides used in crystallization, *i.e.,* TACE as disclosed in Black et al., "A Metalloproteinase disintigrin that releases tumour-necrosis factor-.alpha. from cells," Nature 385: 729-733 (February 1997), with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells (specification at p. 31); the specification discloses only a

single species of the genus of TACE crystals and binding partners thereof, *i.e.,* a crystal of the purified TACE polypeptide described above co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41°; and the specification discloses only a single representative species of crystallization buffers that resulted in a TACE crystal that was suitable for x-ray diffraction, *i.e.,* 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol. The specification fails to disclose any other representative species of the genus of TACE crystals, TACE proteins, and TACE binding partners and also fails to disclose any other representative species of crystallization buffers that can be used to achieve a crystal of TACE polypeptide. Other than these single representative species, the specification fails to disclose any additional species of the genus of compositions, TACE proteins, TACE binding partners, and crystallization buffers, which encompass widely variant species. The genus of compositions encompasses TACE protein crystals of any TACE polypeptide – from any source and having any amino acid sequence that is considered to be a "TACE" polypeptide, optionally liganded with any binding partner, and having any unit cell dimensions. The genus of TACE polypeptides encompasses any TACE polypeptide having any sequence of amino acids, including any mutant and variant TACE polypeptides, including non-functional TACE polypeptides. The genus of TACE binding partners encompasses any protein, antibody, or small molecule inhibitor that binds to a TACE polypeptide. The genus of crystallization buffers encompasses a buffer having any composition. While MPEP § 2163 acknowledges that in certain

situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." It is acknowledged that certain claims limit the TACE polypeptide sequence, the structure of the binding partner, OR the unit cell dimensions. However, even these claims encompass widely variant species, considering that, while a crystal may have a defined space group and a defined sequence, binding partner, or unit cell dimensions, the sequence, binding partner, and/or unit cell dimensions are completely undefined.

Applicant argues claim 15 does not require the crystallization of a crystal that is suitable for x-ray diffraction and has been amended to require the crystallization buffer comprise sodium citrate, which is present in the three buffers used in the crystallization as disclosed in the specification.

Applicant's argument is not found persuasive. The examiner acknowledges that claim 15 does not require production of a crystal that is suitable for x-ray diffraction and further acknowledges the amendment to claim 15 to require sodium citrate in the crystallization buffer. However, as noted above, and undisputed by applicant, the specification discloses only a single representative species of the genus of recited or claimed TACE polypeptides used in crystallization, *i.e.*, TACE as disclosed in Black et al., "A Metalloproteinase disintigrin that releases tumour-necrosis factor-.alpha. from cells," Nature 385: 729-733 (February 1997), with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and

expressed in CHO cells (specification at p. 31); the specification discloses only a single species of the genus of TACE binding partners, *i.e.*, N-[D,L-[2-(hydroxyaminocarnbonyl)m-ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, the specification discloses only three representative species of crystallization buffers with sodium citrate that resulted in a TACE crystal, *i.e.*, 0.1 M sodium citrate, pH 5.0, 40 % v/v ethanol (p. 33, Buffer B); 0.1 M sodium citrate, pH 8.7, 20 % w/v PEG 4000, and 20% v/v isopropanol (p. 33, Buffer C); and 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol (p. 34, Buffer D), and the specification discloses only a single method for TACE crystallization, *i.e.*, Example 2 at pp. 33-34 of the specification. The specification fails to disclose any other representative species of the genus of TACE proteins, TACE binding partners, and crystallization buffers and conditions that can be used to achieve a crystal of TACE polypeptide. Other than these representative species, the specification fails to disclose any additional species of the genus of compositions, TACE proteins, TACE binding partners, and crystallization buffers and conditions, which encompass widely variant species. The method encompasses the use of any TACE polypeptide – from any source and having any amino acid sequence that is considered to be a "TACE" polypeptide, optionally liganded with any binding partner, and having any unit cell dimensions. The genus of TACE polypeptides encompasses any TACE polypeptide having any sequence of amino acids, including any mutant and variant TACE polypeptides, including non-functional TACE polypeptides. The genus of TACE binding partners encompasses any protein, antibody, or small molecule inhibitor that binds to a TACE polypeptide. The genus of crystallization buffers and conditions

encompasses a buffer having any composition including sodium citrate at any concentration and any pH and crystallization under any conditions. It is acknowledged that certain claims limit the TACE polypeptide sequence, the structure of the binding partner, the space group or unit cell dimensions of the resulting crystal, or the composition and concentrations of the crystallization buffer. However, even these claims encompass widely variant species, considering that, while crystallization method may recite the TACE polypeptide sequence, the structure of the binding partner, the space group or unit cell dimensions of the resulting crystal, OR the composition and concentrations of the crystallization buffer, the remaining elements of the method claim are completely undefined.

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[16] The scope of enablement rejection of claim(s) 1-9 and 11-22 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. Newly added claims 28-31 are included in the instant rejection. Thus, claims 1-9, 11-22, and 28-31 are rejected herein.

RESPONSE TO ARGUMENT: Applicant argues the rejection is obviated by amendment to claims 1 and 22 to recite the space group of the claimed crystal.

Addressing the breadth of the claims, applicant argues the crystal claims are limited to having a specific space group and the method claims are limited to use of a crystallization buffer comprising sodium citrate. Regarding the state of the art/level of one of ordinary skill/level of predictability in the art, applicant argues the specification provides guidance for making a TACE crystal having space group $P2_1$ and the claims do not require the crystal to be of diffraction quality. Addressing the amount of direction/working examples, applicant argues the claims are not limited to making crystals that are diffraction quality and demonstrate the use of three buffers that are used to generate TACE crystals and that the disclosure and working examples are sufficient for a skilled artisan to make and use the full scope of the claimed invention. Regarding the quantity of experimentation, applicant argues the application teaches how to make and use crystals of TACE polypeptides. According to applicant, since the polypeptide is disclosed, the recited characteristics are sufficient to describe the genus of claimed crystals in view of Case 4 of the Trilateral Report.

Applicant's argument is not found persuasive. Regarding Case 4 of the Trilateral Report, it is noted that the protein crystal of the claim of Case 4 recites unit cell dimensions, which are not present in the instant claims 1 and 22. Even assuming *arguendo* unit cell dimensions were present in claims 1 and 22, it is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention for reasons that follow. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth

of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The examiner acknowledges the claim amendment to limit the space group of the crystals to $P2_1$ and to require the crystallization buffer to comprise sodium citrate. Claims 1-9, 11-14, 22, and 28-31 are so broad as to encompass crystals having space group $P2_1$ of any TACE polypeptide, having any sequence of amino acids, including any mutant and variant TACE polypeptides, including non-functional TACE polypeptides, optionally liganded with any binding partner having any structure, having any unit cell dimensions. Claims 15-21 are so broad as to encompass a method for crystallizing any TACE polypeptide as noted above optionally liganded with any binding partner, under any crystallization conditions that include a crystallization buffer comprising sodium citrate at any concentration and any pH. The broad scope of claimed crystals and crystallization methods is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to a crystal of a purified TACE protein as disclosed in Black et al. (*supra*) with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells, co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-

alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41° produced according to the method set forth in the specification at pp. 33-34 in the crystallization buffer of 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a **high** level of unpredictability for making a protein crystal with an expectation that the crystal will be of diffraction quality. The reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for

emphasis, p. 2, left column, top). In view of these teachings, there is no expectation that a skilled artisan can use the disclosed crystallization conditions to achieve diffraction quality crystals of other TACE polypeptides. Also, Wiencek (*Ann Rev Biomed Eng* 1:505-534) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). Applicant does not appear to dispute the objective evidence of these references. In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other TACE polypeptides optionally having a desired space group and unit cell dimensions as encompassed by the claims can be achieved using *any* crystallization parameters as encompassed by the claims. Further, it is noted that the asserted utility of the claimed crystal is for determination of the structure of TACE for structure based design of TACE inhibitors (p. 2, first full paragraph), which is undisputed by applicant, and it is highly unpredictable as to whether mutant and variant TACE polypeptides will maintain a three-dimensional structure that is equivalent to wild-type TACE for design of biologically relevant TACE inhibitors.

The amount of direction provided by the inventor; The existence of working examples: As noted above, the specification discloses the utility of the claimed crystal is in the determination of the 3-D structure of TACE (p. 2, first full paragraph), which, as acknowledged by Branden et al. at p. 374, requires a diffraction-quality crystal. Applicant does not dispute this position. In this case, the specification discloses only a single working example of such a diffraction quality crystal and method of making

thereof, *i.e.,* a crystal of a purified TACE protein as disclosed in Black et al. (*supra*) with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells, co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41° produced according to the method set forth in the specification at pp. 33-34 in the crystallization buffer 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol. Other than this single working example of a crystal and method for making, the specification fails to provide guidance for crystallizing other polypeptides as encompassed by the claims with an expectation of obtaining diffraction-quality crystals optionally having the recited space group and/or unit cell dimensions. It should be noted that the claims encompass crystals of mutant and variant TACE polypeptides and the specification fails to provide guidance for using those crystals that do not represent biologically relevant TACE polypeptides. Thus, the guidance and working examples as disclosed in the specification fail to remedy the high level of unpredictability that is supported by the references cited above. As noted above and undisputed by applicant, the specification discloses the use of the claimed crystal as being for determination of the 3-D structure of TACE (p. 2, first full paragraph). While applicant argues the claims do not require diffraction quality crystals, it is noted that the specification fails to provide guidance regarding the use of a TACE crystal that is not of diffraction quality.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, it was not routine in the art to screen all TACE polypeptides having a substantial number of variations and modifications as encompassed by the claims – including those that are inactive – optionally complexed with any ligand for those that will yield diffraction-quality crystals using any crystallization conditions as encompassed by the claims. In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystal and polypeptide compositions as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[17] Status of the claims:

Claims 1-9, 11-22, and 28-31 are pending.

Claims 1-9, 11-22, and 28-31 are rejected.

No claim is in condition for allowance.

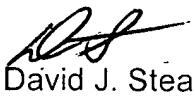
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656